

What is claimed is:

CLAIMS

5 1. A method of modulating the function of a serine/threonine protein kinase with a quinazoline-based compound substituted at the 5-position with an optionally substituted five-membered or six-membered aryl or heteroaryl ring, comprising the step of contacting cells expressing said serine/threonine protein kinase with said compound.

10 2. The method of claim 1, wherein said serine/threonine protein kinase is RAF.

15 3. A method of identifying compounds that modulate the function of serine/threonine protein kinase, comprising the following steps:

- (a) contacting cells expressing said serine/threonine protein kinase with said compound; and
(b) monitoring an effect upon said cells.

20 4. The method of claim 3, wherein said effect is a change or an absence of a change in cell phenotype.

25 5. The method of claim 3, wherein said effect is a change or an absence of a change in cell proliferation.

6. The method of claim 3, wherein said effect is a change or absence of a change in the catalytic activity of the said serine/threonine protein kinase.

5 7. The method of claim 3, wherein said effect is a change or absence of a change in the interaction between said serine/threonine protein kinase with a natural binding partner, as described herein.

10 8. The method of claim 3, comprising the following steps:

(a) lysing said cells to render a lysate comprising serine/threonine protein kinase;

(b) adsorbing said serine/threonine protein kinase to an antibody;

15 (c) incubating said adsorbed serine/threonine protein kinase with a substrate or substrates; and

(d) adsorbing said substrate or substrates to a solid support or antibody;

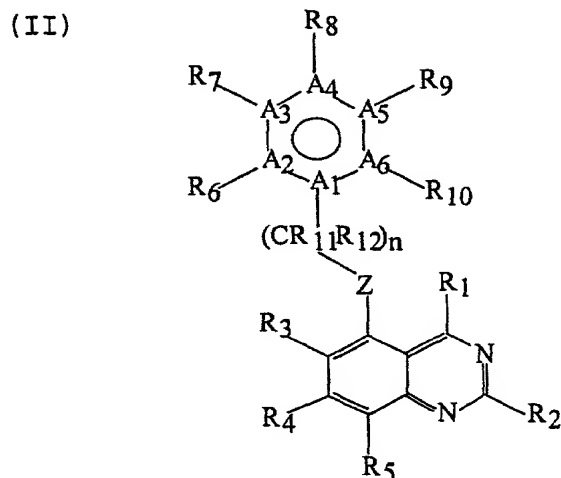
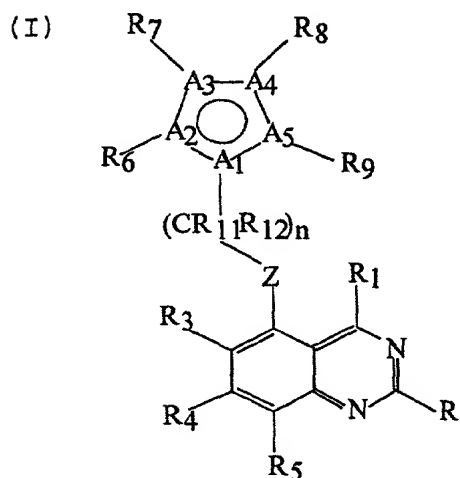
20 wherein said step of monitoring said effect on said cells comprises measuring the phosphate concentration of said substrate or substrates.

25 9. The method of claim 3, wherein said serine/threonine protein kinase is RAF and comprises the following steps:

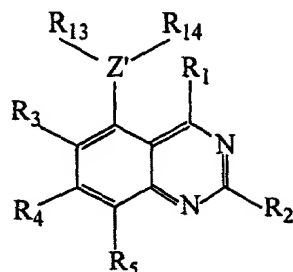
- (a) lysing said cells to render a lysate comprising RAF;
- (b) adsorbing said RAF to an antibody;
- (c) incubating the adsorbed RAF with MEK and MAPK; and
- (d) adsorbing said MEK and MAPK to a solid support or antibody or antibodies;

wherein said step of measuring said effect on said cells comprises monitoring the phosphate concentration of said MEK and MAPK.

10. The method of claim 1, wherein said quinazoline-based compound has the formula set forth in structure I, II, or III:



(III)



wherein

(a) Z is oxygen, NX_1 , or sulfur, where X_1 is selected from the group consisting of hydrogen, saturated or unsaturated alkyl, and five-membered or six-membered aryl or heteroaryl ring moieties;

(b) n is 0, 1, 2, 3, or 4;

(c) A_1 , A_2 , A_3 , A_4 , A_5 , and A_6 are independently selected from the group consisting of carbon, nitrogen, oxygen, and sulfur;

(d) R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , and R_{10} are independently selected from the group consisting of

(i) hydrogen;

(ii) saturated or unsaturated alkyl;

(iii) NX_2X_3 , where X_2 and X_3 are

independently selected from the group consisting of hydrogen, saturated or unsaturated alkyl, and five-membered or six-membered aryl or heteroaryl ring moieties;

(iv) halogen or trihalomethyl;

(v) a ketone of formula $-CO-X_4$, where

X_4 is selected from the group consisting of hydrogen, alkyl, and five-membered or six-membered aryl or heteroaryl moieties;

(vi) a carboxylic acid of formula - $(X_5)_n$ -COOH or ester of formula - $(X_6)_n$ -COO- X_7 , where X_5 , X_6 , and X_7 and are independently selected from the group consisting of alkyl and five-membered or six-membered aryl or heteroaryl moieties and where n is 0 or 1;

(vii) an alcohol of formula $(X_8)_n$ -OH or an alkoxy moiety of formula - $(X_8)_n$ -O- X_9 , where X_8 and X_9 are independently selected from the group consisting of alkyl and five-membered or six-membered aryl or heteroaryl ring moieties and where n is 0 or 1, and where said ring moieties are optionally substituted with one or more substituents selected from the group consisting of alkyl, halogen, trihalomethyl, carboxylate, and ester;

(viii) -NHCOX₁₀, where X_{10} is selected from the group consisting of alkyl, hydroxyl, and five-membered or six-membered aryl or heteroaryl ring moieties, wherein said ring moieties are optionally substituted with one or more substituents selected from the group consisting of alkyl, halogen, trihalomethyl, carboxylate, and ester;

(ix) -SO₂NX₁₁X₁₂, where X_{11} and X_{12} are selected from the group consisting of hydrogen, alkyl, and five-membered or six-membered aryl or heteroaryl ring moieties;

(x) a five-membered or six-membered

aryl or heteroaryl ring moiety optionally substituted with one or more substituents selected from the group consisting of alkyl, halogen, trihalomethyl, carboxylate, and ester moieties;

5 (g) any adjacent R_3 , R_4 , and R_5 or any adjacent R_6 , R_7 , R_8 , R_9 , and R_{10} are fused together to form a five-membered or six-membered aryl or heteroaryl ring moiety, wherein said five-membered or six-membered aryl or heteroaryl ring comprises two carbon atoms of the quinazoline ring;

10 (h) R_{11} and R_{12} are independently selected from the group consisting of

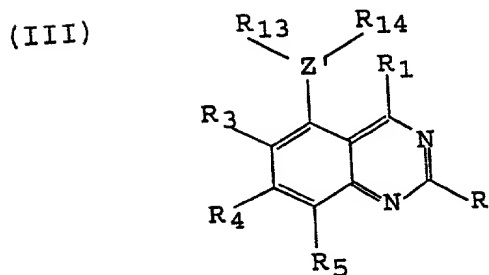
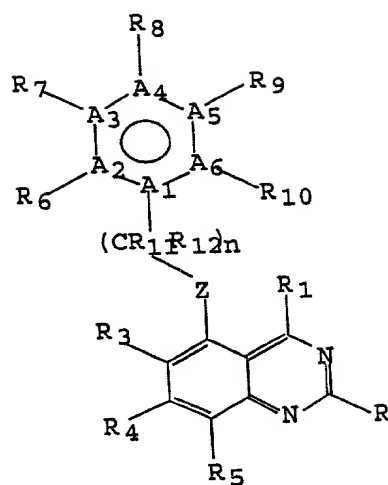
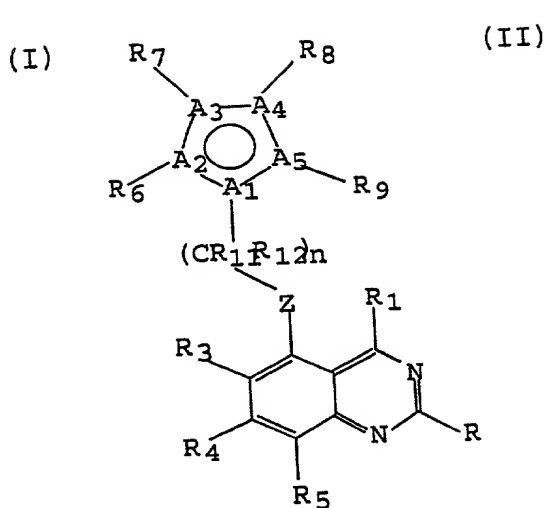
(i) hydrogen;

(ii) saturated or unsaturated alkyl;

and

15 (i) Z' is carbon, oxygen, sulfur, or nitrogen and R_{13} and R_{14} taken together form a five-membered or six-membered heteroaryl ring with Z' as a ring member.

20 11. The method of claim 1, wherein said quinazoline-based compound has the formula set forth in structure I, II, or III:



wherein

(a) Z is oxygen, NX_1 , or sulfur, where X_1 is selected from the group consisting of hydrogen and saturated or unsaturated alkyl;

(b) n is 0, 1, or 2;

(c) A_1 , A_2 , A_3 , A_4 , A_5 , and A_6 are independently

selected from the group consisting of carbon, nitrogen, oxygen, and sulfur;

(d) R_1 and R_2 are independently selected from the group consisting of

- (i) hydrogen;
- (ii) saturated or unsaturated alkyl;
- (iii) NX_2X_3 , where X_2 and X_3 are independently selected from the group consisting of hydrogen and saturated or unsaturated alkyl; and
- (iv) halogen or trihalomethyl;
- (v) five-membered or six-membered aryl or heteroaryl ring moiety;

(e) R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , and R_{10} are independently selected from the group consisting of

- (i) hydrogen;
- (ii) saturated or unsaturated alkyl;
- (iii) NX_4X_5 , where X_4 and X_5 are independently selected from the group consisting of hydrogen and saturated or unsaturated alkyl; and
- (iv) halogen or trihalomethyl;
- (v) $C(X_6)_3$, where X_6 is selected from the group consisting of fluorine, chlorine, bromine, and iodine;
- (vi) OX_7 , where X_7 is selected from the group consisting of hydrogen, saturated or unsaturated alkyl, and a five-membered or six-membered aryl or heteroaryl ring moiety;

(f) any adjacent R_3 , R_4 , and R_5 or any adjacent R_6 , R_7 , R_8 , R_9 , and R_{10} are fused together to form a five-membered or six-membered aryl or heteroaryl ring moiety, wherein said five-membered or six-membered aryl or heteroaryl ring comprises two carbon atoms of the quinazoline ring;

(g) R_{11} and R_{12} are independently selected from the group consisting of

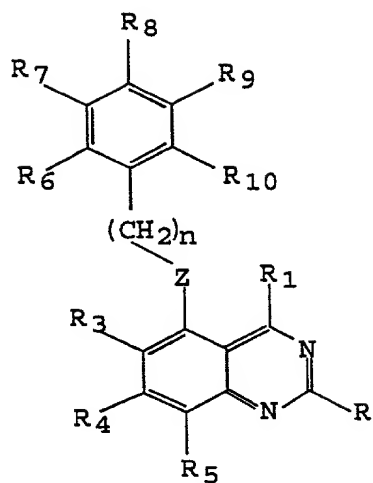
(i) hydrogen; and

(ii) saturated or unsaturated alkyl; and

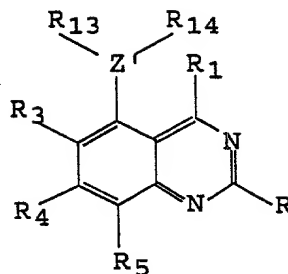
(h) Z' is nitrogen, oxygen, or sulfur and R_{13} and R_{14} taken together form a five-membered or six-membered heteroaryl ring moiety with Z' as a ring member, wherein said ring is optionally substituted with one, two, or three alkyl, halogen, trihalomethyl, carboxylate, and ester moieties.

12. The method of claim 1, wherein said quinazoline-based compound has the structure set forth in formula IV or V:

(IV)



(V)



wherein

- (a) Z is oxygen or sulfur;
- (b) n is 0 or 1;
- (c) R₁ and R₂ are independently selected from

the group consisting of

- (i) hydrogen; and
- (ii) NX₁X₂, where X₁ and X₂ are

independently selected from the group consisting of
hydrogen and saturated or unsaturated alkyl;

- (iii) benzyl;

(d) R₃, R₄, and R₅ are independently selected
from the group consisting of

- (i) hydrogen; and

(ii) saturated or unsaturated alkyl;

(iii) NX_3X_4 , where X_3 and X_4 are independently selected from the group consisting of hydrogen and saturated or unsaturated alkyl;

(e) R_6 , R_7 , R_8 , R_9 , and R_{10} are independently selected from the group consisting of

(i) hydrogen;

(ii) saturated or unsaturated alkyl;

(iii) NX_5X_6 , where X_5 and X_6 are independently selected from the group consisting of hydrogen and saturated or unsaturated alkyl; and

(iv) halogen or trihalomethyl;

(v) $C(X_7)_3$, where X_7 is selected from the group consisting of fluorine, chlorine, bromine, and iodine; and

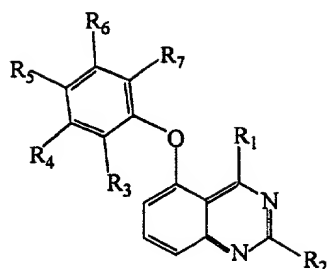
(vi) methoxy;

(f) R_{11} and R_{12} are hydrogen; and

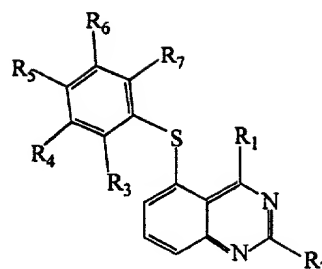
(g) Z' is nitrogen and R_{13} and R_{14} taken together form a five-membered heteroaryl ring.

13. The method of claim 1, wherein said quinazoline-based compound has a structure set forth in formula VI or VII:

(VI)



(VII)



wherein

(a) R_1 and R_2 are independently selected from the group consisting of hydrogen and $-NH_2$, provided at least one of R_1 and R_2 is $-NH_2$;

(b) R_3 , R_4 , R_5 , R_6 , and R_7 are independently selected from the group consisting of

- (i) hydrogen;
- (ii) saturated or unsaturated alkyl;
- (iii) NX_4X_5 , where X_4 and X_5 are independently

selected from the group consisting of hydrogen and saturated or unsaturated alkyl; and

- (iv) halogen;
- (v) $C(X_6)_3$, where X_6 is selected from the

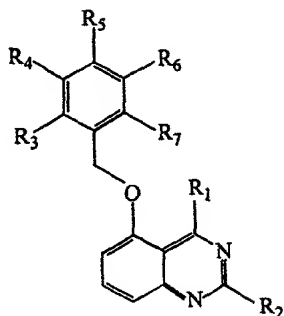
group consisting of fluorine, chlorine, bromine, and iodine; and

- (vi) OX_7 , where X_7 is selected from the

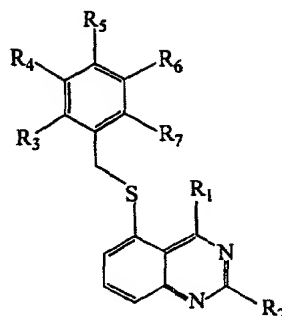
group consisting of hydrogen, saturated or unsaturated alkyl, and a five-membered or six-membered aryl or heteroaryl ring moiety.

14. The method of claim 1, wherein said quinazoline-based compound has a structure set forth in formula VIII or IX:

(VIII)



(IX)



wherein

(a) R₁ and R₂ are independently selected from the group consisting of hydrogen and -NH₂, provided at least one of R₁ and R₂ is -NH₂;

(b) R₃, R₄, R₅, R₆, and R₇ are independently selected from the group consisting of

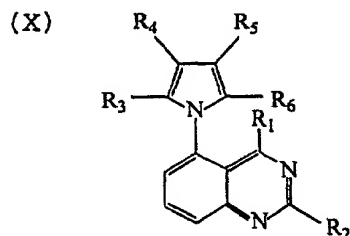
- (i) hydrogen;
- (ii) saturated or unsaturated alkyl;
- (iii) NX₄X₅, where X₄ and X₅ are independently selected from the group consisting of hydrogen and saturated or unsaturated alkyl; and
- (iv) halogen;
- (v) C(X₆)₃, where X₆ is selected from the group consisting of fluorine, chlorine, bromine, and

iodine; and

(vi) OX_7 , where X_7 is selected from the group consisting of hydrogen, saturated or unsaturated alkyl, and a five-membered or six-membered aryl or heteroaryl ring moiety.

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15. The method of claim 1, wherein said quinazoline-based compound has a structure set forth in formula X:



wherein

(a) R_1 and R_2 are independently selected from the group consisting of hydrogen and $-NH_2$, provided at least one of R_1 and R_2 is $-NH_2$;

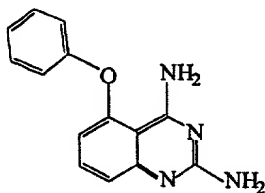
(b) R_3 , R_4 , R_5 , and R_6 are independently selected from the group consisting of

- (i) hydrogen;
- (ii) saturated or unsaturated alkyl;
- (iii) NX_4X_5 , where X_4 and X_5 are independently selected from the group consisting of hydrogen and saturated or unsaturated alkyl; and

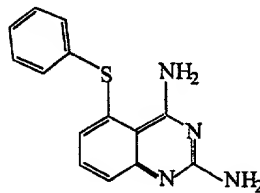
- (iv) halogen;
- (v) $C(X_6)_3$, where X_6 is selected from the group consisting of fluorine, chlorine, bromine, and iodine; and
- (vi) OX_7 , where X_7 is selected from the group consisting of hydrogen, saturated or unsaturated alkyl, and a five-membered or six-membered aryl or heteroaryl ring moiety.

16. The method of claim 1, wherein said quinazoline-based compound is selected from the group consisting of:

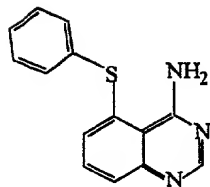
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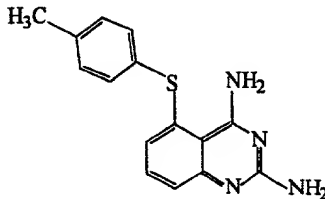
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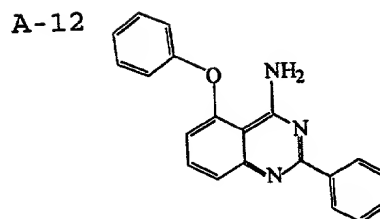
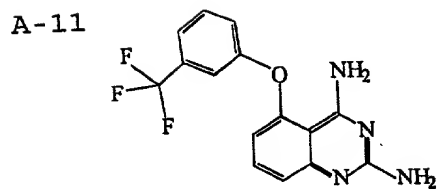
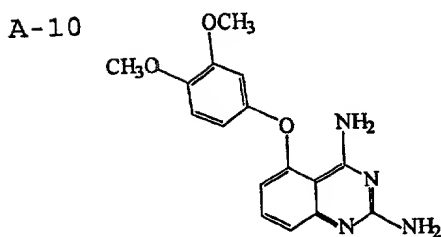
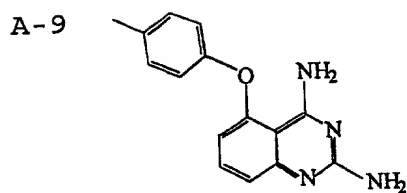
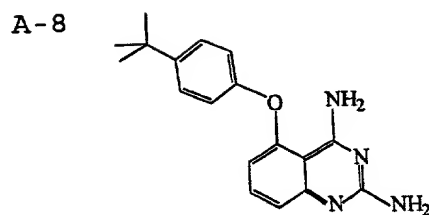
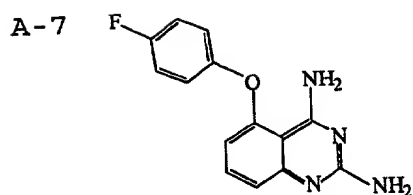
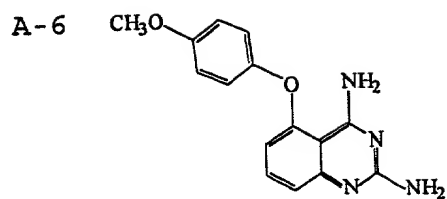
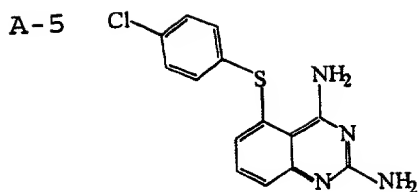


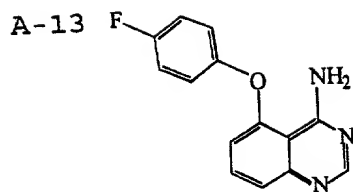
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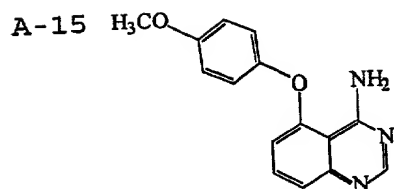
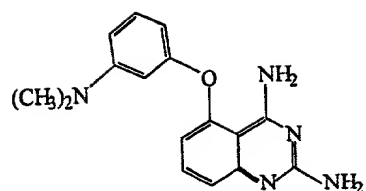
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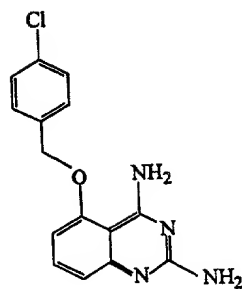




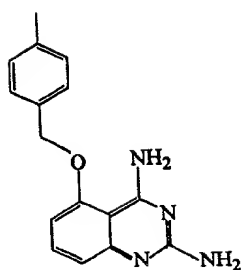
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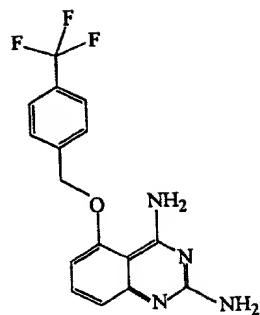
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A-17

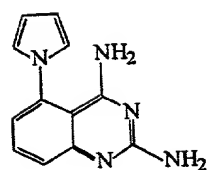


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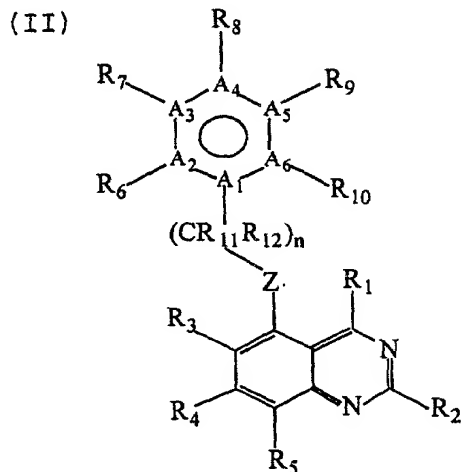
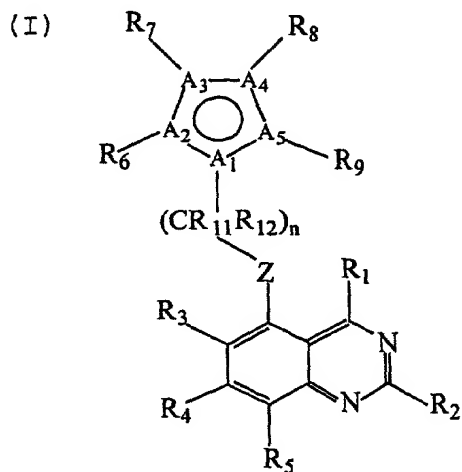


and

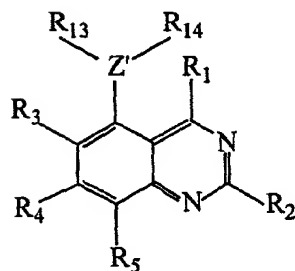
A-19



17. A method of preventing or treating an abnormal condition in an organism, comprising the step of administering a quinazoline-based compound of formula I, II, or III to said organism:



(III)



wherein

(a) Z is oxygen, NX_1 , or sulfur, where X_1 is selected from the group consisting of hydrogen, saturated or unsaturated alkyl, and five-membered or six-membered aryl or heteroaryl ring moieties;

(b) n is 0, 1, 2, 3, or 4;

(c) A_1 , A_2 , A_3 , A_4 , A_5 , and A_6 are independently selected from the group consisting of carbon, nitrogen, oxygen, and sulfur;

(d) R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , and R_{10} are independently selected from the group consisting of

(i) hydrogen;

(ii) saturated or unsaturated alkyl;

(iii) NX_2X_3 , where X_2 and X_3 are independently selected from the group consisting of hydrogen, saturated or unsaturated alkyl, and five-membered or six-membered aryl or heteroaryl ring moieties;

(iv) halogen or trihalomethyl;

(v) a ketone of formula $-CO-X_4$, where X_4 is selected from the group consisting of hydrogen, alkyl, and five-membered or six-membered aryl or heteroaryl moieties;

(vi) a carboxylic acid of formula $-(X_5)_n-COOH$ or ester of formula $-(X_5)_n-COO-X_7$, where X_5 , X_6 , and X_7 are independently selected from the group consisting of alkyl and five-membered or six-membered aryl or heteroaryl moieties and where n is 0 or 1;

(vii) an alcohol of formula $(X_8)_n-OH$ or an alkoxy moiety of formula $-(X_8)_n-O-X_9$, where X_8 and X_9 are

independently selected from the group consisting of alkyl and five-membered or six-membered aryl or heteroaryl ring moieties and where n is 0 or 1, and where said ring moieties are optionally substituted with one or more substituents selected from the group consisting of alkyl, halogen, trihalomethyl, carboxylate, and ester;

(viii) -NHCox_{10} , where X_{10} is selected from the group consisting of alkyl, hydroxyl, and five-membered or six-membered aryl or heteroaryl ring moieties, wherein said ring moieties are optionally substituted with one or more substituents selected from the group consisting of alkyl, halogen, trihalomethyl, carboxylate, and ester;

(ix) $\text{-SO}_2\text{NX}_{11}\text{X}_{12}$, where X_{11} and X_{12} are selected from the group consisting of hydrogen, alkyl, and five-membered or six-membered aryl or heteroaryl ring moieties;

(x) a five-membered or six-membered aryl or heteroaryl ring moiety optionally substituted with one or more substituents selected from the group consisting of alkyl, halogen, trihalomethyl, carboxylate, and ester moieties;

(e) any adjacent R_3 , R_4 , and R_5 or any adjacent R_6 , R_7 , R_8 , R_9 , and R_{10} are fused together to form a five-membered or six-membered aryl or heteroaryl ring moiety, wherein said five-membered or six-membered aryl or heteroaryl ring comprises two carbon atoms of the quinazoline ring;

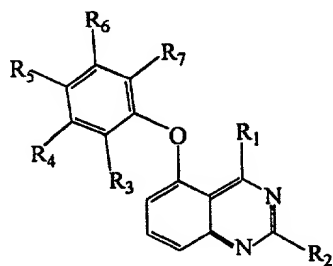
(f) R_{11} and R_{12} are independently selected from the group consisting of

- (i) hydrogen;
- (ii) saturated or unsaturated alkyl;

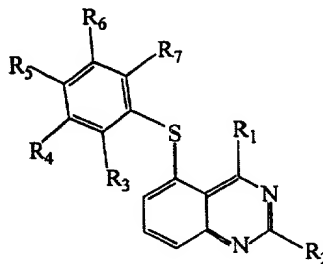
(g) Z' is carbon, oxygen, sulfur, or nitrogen and R_{13} and R_{14} taken together form a five-membered or six-membered heteroaryl ring with Z' as a ring member.

18. The method of claim 17, wherein said quinazoline-based compound has a structure set forth in formula VI or VII:

(VI)



(VII)



where

(a) R_1 and R_2 are independently selected from the group consisting of hydrogen and $-NH_2$, provided at least one of R_1 and R_2 is $-NH_2$;

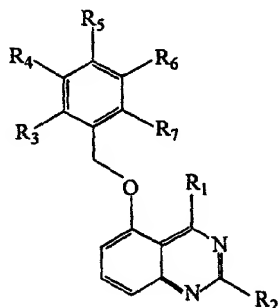
(b) R_3 , R_4 , R_5 , R_6 , and R_7 are independently selected from the group consisting of

- (i) hydrogen;

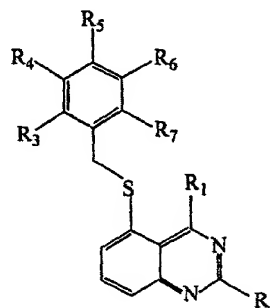
- (ii) saturated or unsaturated alkyl;
- (iii) NX_4X_5 , where X_4 and X_5 are independently selected from the group consisting of hydrogen and saturated or unsaturated alkyl; and
- (iv) halogen;
- (v) $C(X_6)_3$, where X_6 is selected from the group consisting of fluorine, chlorine, bromine, and iodine; and
- (vi) OX_7 , where X_7 is selected from the group consisting of hydrogen, saturated or unsaturated alkyl, and a five-membered or six-membered aryl or heteroaryl ring moiety.

19. The method of claim 17, wherein said quinazoline-based compound has a structure set forth in formula VIII or IX:

(VIII)



(IX)



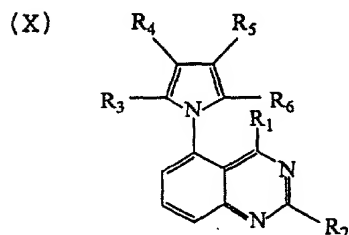
where

(a) R_1 and R_2 are independently selected from the group consisting of hydrogen and $-NH_2$, provided at least one of R_1 and R_2 is $-NH_2$;

(b) R_3 , R_4 , R_5 , R_6 , and R_7 are independently selected from the group consisting of

- 5 (i) hydrogen;
- (ii) saturated or unsaturated alkyl;
- (iii) NX_4X_5 , where X_4 and X_5 are independently selected from the group consisting of hydrogen and saturated or unsaturated alkyl; and
- 10 (iv) halogen;
- (v) $C(X_6)_3$, where X_6 is selected from the group consisting of fluorine, chlorine, bromine, and iodine; and
- 15 (vi) OX_7 , where X_7 is selected from the group consisting of hydrogen, saturated or unsaturated alkyl, and a five-membered or six-membered aryl or heteroaryl ring moiety.

20 20. The method of claim 17, wherein said quinazoline-based compound has a structure set forth in formula X:



wherein

(a) R_1 and R_2 are independently selected from the group consisting of hydrogen and $-NH_2$, provided at least one of R_1 and R_2 is $-NH_2$;

(b) R_3 , R_4 , R_5 , and R_6 are independently selected from the group consisting of

- (i) hydrogen;
- (ii) saturated or unsaturated alkyl;
- (iii) NX_4X_5 , where X_4 and X_5 are independently selected from the group consisting of hydrogen and saturated or unsaturated alkyl; and
- (iv) halogen;
- (v) $C(X_6)_3$, where X_6 is selected from the group consisting of fluorine, chlorine, bromine, and iodine; and
- (vi) OX_7 , where X_7 is selected from the group consisting of hydrogen, saturated or unsaturated alkyl, and a five-membered or six-membered aryl or heteroaryl ring moiety.

21. The method of claim 17, wherein said organism is a mammal.

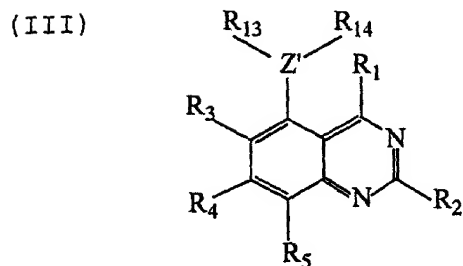
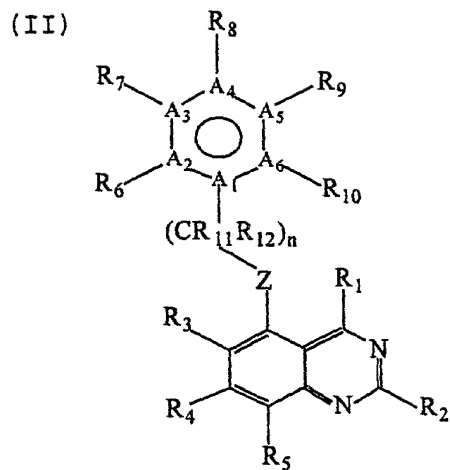
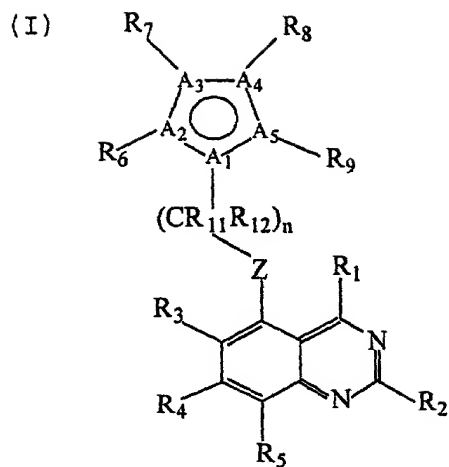
22. The method of claim 17, wherein said abnormal condition is cancer or a fibrotic disorder.

23. The method of claim 22, wherein said abnormal condition is a cancer selected from the group consisting of lung cancer, ovarian cancer, breast cancer, brain cancer, intra-axial brain cancer, colon cancer, prostate cancer, Kaposi's sarcoma, melanoma, and glioma.

24. The method of claim 17, wherein said abnormal condition is associated with an aberration in a signal transduction pathway characterized by an interaction between a serine/threonine protein kinase and a natural binding partner.

25. The method of claim 24, wherein said serine/threonine protein kinase is RAF.

26. A quinazoline compound having a structure set forth in formula I, II, or III:



wherein

- (i) Z is oxygen, NX_1 , or sulfur, where X_1 is selected from the group consisting of hydrogen, saturated or unsaturated alkyl, and five-membered or six-membered aryl or heteroaryl ring moieties;

(iii) $A_1, A_2, A_3, A_4, A_5,$ and A_6 are independently selected from the group consisting of carbon, nitrogen, oxygen, and sulfur;

(iv) R_1 and R_2 are independently selected from the group consisting of

- 5 (a) hydrogen;
- (b) saturated or unsaturated alkyl;
- (c) NX_2X_3 , where X_2 and X_3 are independently selected from the group consisting of hydrogen and saturated or unsaturated alkyl; and
- 10 (d) halogen or trihalomethyl;
- (e) five-membered or six-membered aryl or heteroaryl ring moiety;

(v) $R_3, R_4, R_5, R_6, R_7, R_8, R_9,$ and R_{10} are independently selected from the group consisting of:

15 (a) hydrogen, provided that at least one of $R_3, R_4, R_5, R_6, R_7, R_8, R_9,$ and R_{10} is a non-hydrogen moiety if R_2 is $-NH_2$;

(b) saturated or unsaturated alkyl, wherein said R_8 is not methyl when R_2 is $-NH_2$ and when $n = 1$;

20 (c) NX_2X_3 , where X_2 and X_3 are independently selected from the group consisting of hydrogen, saturated or unsaturated alkyl, and five-membered or six-membered aryl or heteroaryl ring moieties;

(d) halogen or trihalomethyl, wherein said R_8 is not chlorine or fluorine when R_2 is $-NH_2$ and when $n = 1$;

25

(e) a ketone of formula -CO-X_4 , where X_4 is selected from the group consisting of hydrogen, alkyl, and five-membered or six-membered aryl or heteroaryl moieties;

(f) a carboxylic acid of formula $\text{-(X}_5\text{)}_n\text{-COOH}$ or ester of formula $\text{-(X}_6\text{)}_n\text{-COO-X}_7$, where X_5 , X_6 , and X_7 are independently selected from the group consisting of alkyl and five-membered or six-membered aryl or heteroaryl moieties and where n is 0 or 1;

(g) an alcohol of formula $\text{(X}_8\text{)}_n\text{-OH}$ or an alkoxy moiety of formula $\text{-(X}_8\text{)}_n\text{-O-X}_9$, where X_8 and X_9 are independently selected from the group consisting of alkyl and five-membered or six-membered aryl or heteroaryl ring moieties and where n is 0 or 1, and wherein said ring moieties are optionally substituted with one or more substituents selected from the group consisting of alkyl, halogen, trihalomethyl, carboxylate, and ester;

(h) -NHCOX_{10} , where X_{10} is selected from the group consisting of alkyl, hydroxyl, and five-membered or six-membered aryl or heteroaryl ring moieties, wherein said ring moieties are optionally substituted with one or more substituents selected from the group consisting of alkyl, halogen, trihalomethyl, carboxylate, and ester;

(i) $\text{-SO}_2\text{NX}_{11}\text{X}_{12}$, where X_{11} and X_{12} are selected from the group consisting of hydrogen, alkyl, and five-membered or six-membered aryl or heteroaryl ring moieties;

(j) a five-membered or six-membered aryl or heteroaryl ring moiety optionally substituted with one or more substituents selected from the group consisting of alkyl, halogen, trihalomethyl, carboxylate, and ester moieties;

5 (v) any adjacent R_3 , R_4 , and R_5 or any adjacent R_6 , R_7 , R_8 , R_9 , and R_{10} are fused together to form a five-membered or six-membered aryl or heteroaryl ring moiety, wherein said five-membered or six-membered aryl or heteroaryl ring comprises two carbon atoms of the quinazoline ring;

10 (vi) R_{11} and R_{12} are independently selected from the group consisting of

(a) hydrogen;

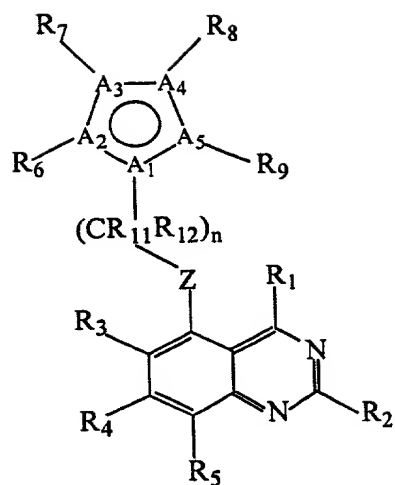
(b) saturated or unsaturated alkyl;

15 and

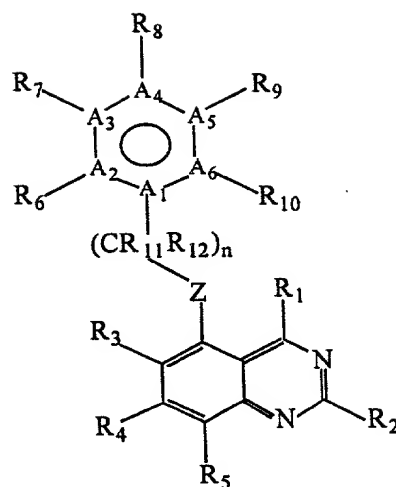
(vii) Z' is carbon, oxygen, sulfur, or nitrogen and R_{13} and R_{14} taken together form a five-membered or six-membered heteroaryl ring with Z' as a ring member.

20 27. A quinazoline compound having the structure set forth in formula I, II, or III:

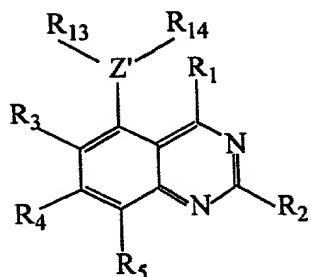
(I)



(II)



(III)



wherein

(a) Z is oxygen, NX₁, or sulfur, where X₁ is selected from the group consisting of hydrogen and saturated or unsaturated alkyl;

(b) n is 0, 1, or 2;

(c) A_1 , A_2 , A_3 , A_4 , A_5 , and A_6 are independently selected from the group consisting of carbon, nitrogen, oxygen, and sulfur;

(d) R_1 and R_2 are independently selected from the group consisting of

- 5 (i) hydrogen;
- (ii) saturated or unsaturated alkyl;
- (iii) NX_2X_3 , where X_2 and X_3 are independently selected from the group consisting of hydrogen and saturated or unsaturated alkyl; and
- 10 (iv) halogen or trihalomethyl;
- (v) five-membered or six-membered aryl or heteroaryl ring moiety;

(e) R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , and R_{10} are independently selected from the group consisting of:

15 (i) hydrogen, provided that at least one of R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , and R_{10} is a non-hydrogen moiety if R_2 is $-NH_2$;

(ii) saturated or unsaturated alkyl, wherein said R_8 is not methyl when R_2 is $-NH_2$ and when $n =$

20 1;

(iii) NX_4X_5 , where X_4 and X_5 are independently selected from the group consisting of hydrogen and saturated or unsaturated alkyl; and

25 (iv) halogen or trihalomethyl, wherein said R_8 is not chlorine or fluorine when R_2 is $-NH_2$ and when $n = 1$;

(v) $C(X_6)_3$, where X_6 is selected from the group consisting of fluorine, chlorine, bromine, and iodine;

(vi) OX_7 , where X_7 is selected from the group consisting of hydrogen, saturated or unsaturated alkyl, and a five-membered or six-membered aryl or heteroaryl ring moiety;

(f) any adjacent R_3 , R_4 , and R_5 or any adjacent R_6 , R_7 , R_8 , R_9 , and R_{10} are fused together to form a five-membered or six-membered aryl or heteroaryl ring moiety, wherein said five-membered or six-membered aryl or heteroaryl ring comprises two carbon atoms of the quinazoline ring;

(g) R_{11} and R_{12} are independently selected from the group consisting of

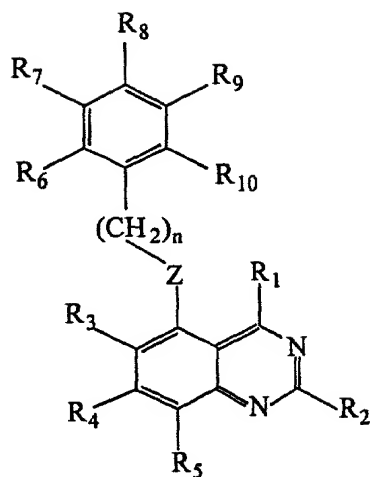
(i) hydrogen; and

(ii) saturated or unsaturated alkyl; and

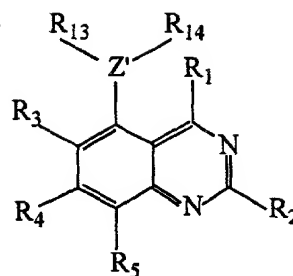
(h) Z' is nitrogen, oxygen, or sulfur and R_{13} and R_{14} taken together form a five-membered or six-membered heteroaryl ring moiety with Z' as a ring member, wherein said ring is optionally substituted with one, two, or three alkyl, halogen, trihalomethyl, carboxylate, and ester moieties.

28. A quinazoline compound having the structure set forth in formula IV or V:

(IV)



(V)



wherein

- (a) Z is oxygen or sulfur;
- (b) n is 0 or 1;
- (c) R_1 and R_2 are independently selected from

the group consisting of

- (i) hydrogen; and
- (ii) NX_1X_2 , where X_1 and X_2 are

independently selected from the group consisting of
hydrogen and saturated or unsaturated alkyl;

- (iii) benzyl;

(d) R_3 , R_4 , and R_5 are independently selected
from the group consisting of

- (i) hydrogen; and

(ii) saturated or unsaturated alkyl;

(iii) NX_3X_4 , where X_3 and X_4 are independently selected from the group consisting of hydrogen and saturated or unsaturated alkyl;

(e) $R_3, R_4, R_5, R_6, R_7, R_8, R_9$, and R_{10} are independently selected from the group consisting of:

(i) hydrogen, provided that at least one of $R_3, R_4, R_5, R_6, R_7, R_8, R_9$, and R_{10} is a non-hydrogen moiety if R_2 is $-NH_2$;

(ii) saturated or unsaturated alkyl, wherein said R_8 is not methyl when R_2 is $-NH_2$ and when $n = 1$;

(iii) NX_5X_6 , where X_5 and X_6 are independently selected from the group consisting of hydrogen and saturated or unsaturated alkyl; and

(iv) halogen or trihalomethyl, wherein said R_8 is not chlorine or fluorine when R_2 is $-NH_2$ and when $n = 1$

(v) $C(X_7)_3$, where X_7 is selected from the group consisting of fluorine, chlorine, bromine, and iodine; and

(vi) methoxy;

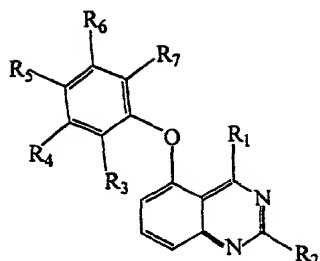
(f) R_{11} and R_{12} are hydrogen; and

(g) Z' is nitrogen and R_{13} and R_{14} taken together form a five-membered heteroaryl ring.

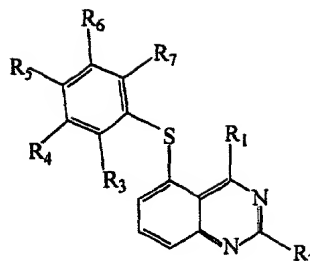
29. A quinazoline compound having a structure set

forth in formula VI or VII:

(VI)



(VII)



wherein

(a) R_1 and R_2 are independently selected from the group consisting of hydrogen and $-NH_2$, provided at least one of R_1 and R_2 is $-NH_2$;

(b) R_3 , R_4 , R_5 , R_6 , and R_7 are independently selected from the group consisting of

(i) hydrogen, provided that at least one of R_3 , R_4 , R_5 , R_6 , and R_7 is a non-hydrogen moiety if R_2 is $-NH_2$;

(ii) saturated or unsaturated alkyl, wherein said R_5 is not methyl when R_2 is $-NH_2$;

(iii) NX_4X_5 , where X_4 and X_5 are independently selected from the group consisting of hydrogen and saturated or unsaturated alkyl; and

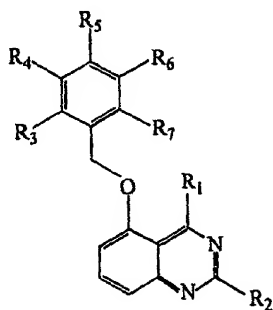
(iv) halogen, wherein said R_5 is not chlorine or fluorine when R_2 is $-NH_2$;

(v) $C(X_6)_3$, where X_6 is selected from the group consisting of fluorine, chlorine, bromine, and iodine; and

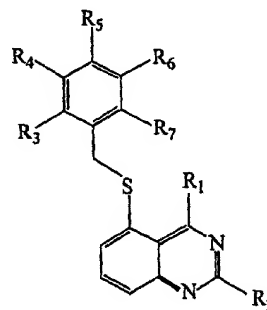
(vi) OX_7 , where X_7 is selected from the group consisting of hydrogen, saturated or unsaturated alkyl, and a five-membered or six-membered aryl or heteroaryl ring moiety.

30. A quinazoline compound having a structure set forth in formula VIII or IX:

(VIII)



(IX)



wherein

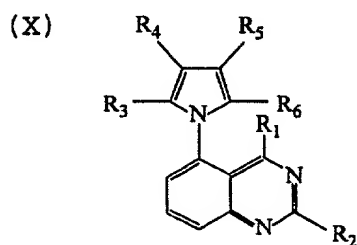
(a) R_1 and R_2 are independently selected from the group consisting of hydrogen and $-NH_2$, provided at least one of R_1 and R_2 is $-NH_2$;

(b) R_3 , R_4 , R_5 , R_6 , and R_7 are independently selected from the group consisting of

(i) hydrogen;

- (ii) saturated or unsaturated alkyl;
- (iii) NX_4X_5 , where X_4 and X_5 are independently selected from the group consisting of hydrogen and saturated or unsaturated alkyl; and
- (iv) halogen;
- (v) $C(X_6)_3$, where X_6 is selected from the group consisting of fluorine, chlorine, bromine, and iodine; and
- (vi) OX_7 , where X_7 is selected from the group consisting of hydrogen, saturated or unsaturated alkyl, and a five-membered or six-membered aryl or heteroaryl ring moiety.

31. A quinazoline compound having a structure set forth in formula X:



wherein

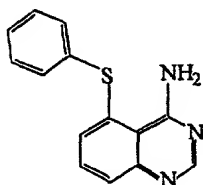
- (a) R_1 and R_2 are independently selected from the group consisting of hydrogen and $-NH_2$, provided at least one of R_1 and R_2 is $-NH_2$;

(b) R_3 , R_4 , R_5 , and R_6 are independently selected from the group consisting of

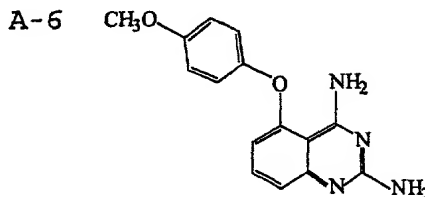
- (i) hydrogen;
- (ii) saturated or unsaturated alkyl;
- (iii) NX_4X_5 , where X_4 and X_5 are independently selected from the group consisting of hydrogen and saturated or unsaturated alkyl; and
- (iv) halogen;
- (v) $C(X_6)_3$, where X_6 is selected from the group consisting of fluorine, chlorine, bromine, and iodine; and
- (vi) OX_7 , where X_7 is selected from the group consisting of hydrogen, saturated or unsaturated alkyl, and a five-membered or six-membered aryl or heteroaryl ring moiety.

32. A quinazoline compound selected from the group consisting of:

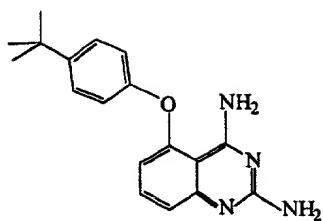
A-3



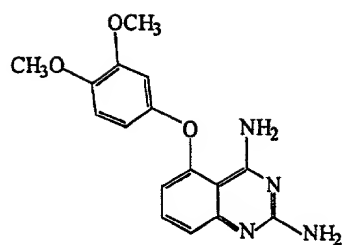
A-6



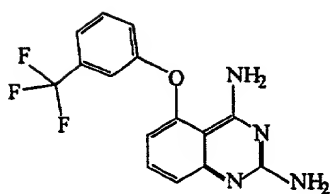
A-8



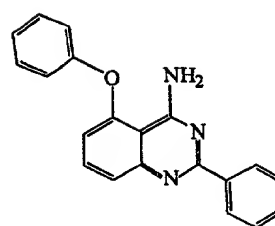
A-10



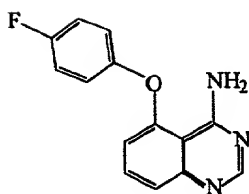
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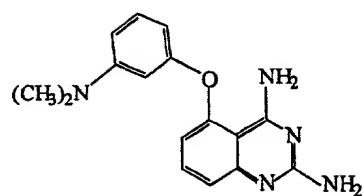
A-12



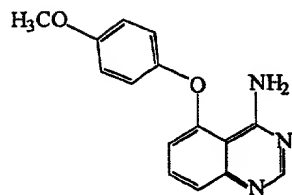
A-13



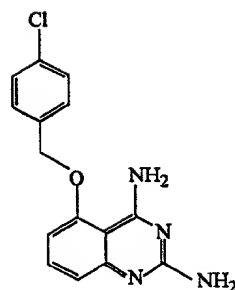
A-14



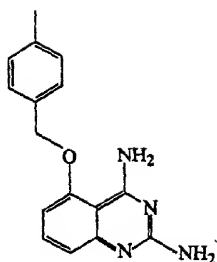
A-15



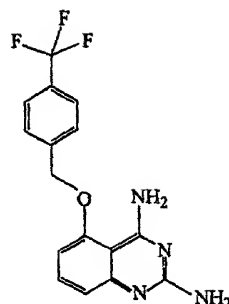
A-16



A-17

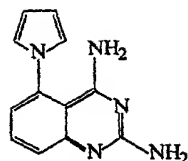


A-18



and

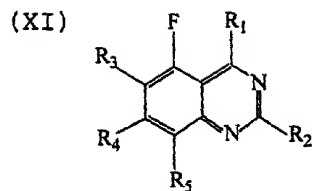
A-19



33. A pharmaceutical composition comprising a
 5 quinazoline compound of any one of claims 26-32 or salt
 thereof, and a physiologically acceptable carrier or
 diluent.

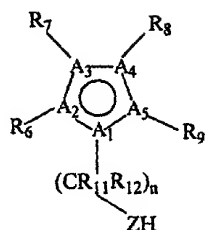
34. A method for synthesizing a compound of claim 26,
 10 comprising the steps of:

(a) reacting a first reactant with a second
 reactant to yield said compound, wherein said first
 reactant has a structure of formula XI:

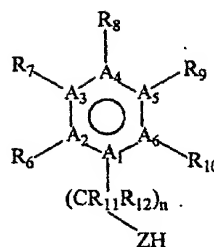


and wherein said second structure has a structure of
formula (XII) or (XIII):

(XII)



(XIII)



5

wherein,

- (a) Z is oxygen or sulfur;
- (b) n is 0, 1, 2, 3, or 4;
- (c) A₁, A₂, A₃, A₄, A₅, and A₆ are independently

selected from the group consisting of carbon, nitrogen,
oxygen, and sulfur;

10

(d) R₁ and R₂ are independently selected from
the group consisting of

- (i) hydrogen;
- (ii) saturated or unsaturated alkyl;
- (iii) NX₂X₃, where X₂ and X₃ are independently

15

selected from the group consisting of hydrogen and saturated or unsaturated alkyl; and

(iv) halogen or trihalomethyl;

(v) five-membered or six-membered aryl or heteroaryl ring moiety;

5 (e) R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , and R_{10} are independently selected from the group consisting of:

(i) hydrogen, provided that at least one of R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , and R_{10} is a non-hydrogen moiety if R_2 is $-NH_2$;

10 (ii) saturated or unsaturated alkyl, wherein said R_8 is not methyl when R_2 is $-NH_2$ and when $n = 1$;

(iii) NX_2X_3 , where X_2 and X_3 are independently selected from the group consisting of hydrogen, saturated or unsaturated alkyl, and five-membered or six-membered aryl or heteroaryl ring moieties;

15 (iv) halogen or trihalomethyl, wherein said R_8 is not chlorine or fluorine when R_2 is $-NH_2$ and when $n = 1$;

20 (v) a ketone of formula $-CO-X_4$, where X_4 is selected from the group consisting of hydrogen, alkyl, and five-membered or six-membered aryl or heteroaryl moieties;

25 (vi) a carboxylic acid of formula $-(X_5)_n-COOH$ or ester of formula $-(X_5)_n-COO-X_7$, where X_5 , X_6 , and X_7 and are independently selected from the group consisting of alkyl and five-membered or six-membered aryl or heteroaryl moieties and where n is 0 or 1;

(vii) an alcohol of formula $(X_8)_n\text{-OH}$ or an alkoxy moiety of formula $-(X_8)_n\text{-O-X}_9$, where X_8 and X_9 are independently selected from the group consisting of alkyl and five-membered or six-membered aryl or heteroaryl ring moieties and where n is 0 or 1, and wherein said ring moieties are optionally substituted with one or more substituents selected from the group consisting of alkyl, halogen, trihalomethyl, carboxylate, and ester;

(viii) -NHCOX_{10} , where X_{10} is selected from the group consisting of alkyl, hydroxyl, and five-membered or six-membered aryl or heteroaryl ring moieties, wherein said ring moieties are optionally substituted with one or more substituents selected from the group consisting of alkyl, halogen, trihalomethyl, carboxylate, and ester;

(ix) $\text{-SO}_2\text{NX}_{11}\text{X}_{12}$, where X_{11} and X_{12} are selected from the group consisting of hydrogen, alkyl, and five-membered or six-membered aryl or heteroaryl ring moieties;

(x) a five-membered or six-membered aryl or heteroaryl ring moiety optionally substituted with one or more substituents selected from the group consisting of alkyl, halogen, trihalomethyl, carboxylate, and ester moieties;

(f) any adjacent R_3 , R_4 , and R_5 or any adjacent R_6 , R_7 , R_8 , R_9 , and R_{10} are fused together to form a five-membered or six-membered aryl or heteroaryl ring moiety, wherein said five-membered or six-membered aryl or

heteroaryl ring comprises two carbon atoms of the quinazoline ring;

(g) R_{11} and R_{12} are independently selected from the group consisting of

(i) hydrogen;

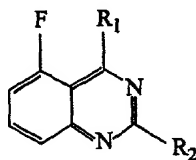
(ii) saturated or unsaturated alkyl; and

(b) collecting a precipitate comprising said compound.

35. A method for synthesizing a compound of claim 29, comprising the steps of:

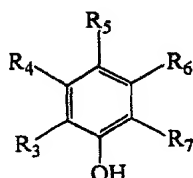
(a) reacting a first reactant with a second reactant yielding said compound, wherein said first reactant has a structure of formula XIV:

(XIV)

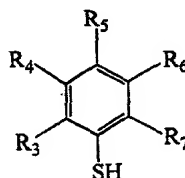


and wherein said second reactant has a structure of formula XV or XVI:

(XV)



(XVI)



wherein,

(a) R_1 and R_2 are independently selected from the group consisting of hydrogen and $-NH_2$, provided at least one of R_1 and R_2 is $-NH_2$;

(b) R_3 , R_4 , R_5 , R_6 , and R_7 are independently selected from the group consisting of

(i) hydrogen, provided that at least one of R_3 , R_4 , R_5 , R_6 , and R_7 is a non-hydrogen moiety if R_2 is $-NH_2$;

(ii) saturated or unsaturated alkyl, wherein said R_5 is not methyl when R_2 is $-NH_2$;

(iii) NX_4X_5 , where X_4 and X_5 are independently selected from the group consisting of hydrogen and saturated or unsaturated alkyl; and

(iv) halogen, wherein said R_5 is not chlorine or fluorine when R_2 is $-NH_2$;

(v) $C(X_6)_3$, where X_6 is selected from the group consisting of fluorine, chlorine, bromine, and iodine; and

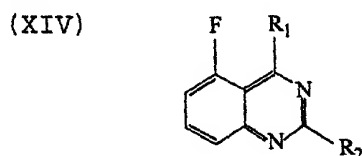
(vi) OX_7 , where X_7 is selected from the group consisting of hydrogen, saturated or unsaturated alkyl, and a five-membered or six-membered aryl or heteroaryl ring moiety; and

(b) collecting a precipitate comprising said compound.

36. A method for synthesizing a compound of claim 28,

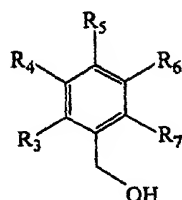
comprising the steps of:

(a) reacting a first reactant with a second reactant yielding said compound, wherein said first reactant has a structure of formula XIV:

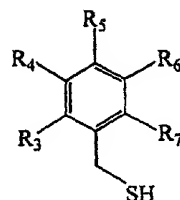


and wherein said second reactant has a structure of formula XVII or XIII:

(XVII)



(XIII)



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wherein,

(a) R_1 and R_2 are independently selected from the group consisting of hydrogen and $-NH_2$, provided at least one of R_1 and R_2 is $-NH_2$;

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(b) R_3 , R_4 , R_5 , R_6 , and R_7 are independently selected from the group consisting of

(i) hydrogen, provided that at least one of R_3 , R_4 , R_5 , R_6 , and R_7 is a non-hydrogen moiety if R_2 is

-NH₂;

(ii) saturated or unsaturated alkyl, wherein said R₅ is not methyl when R₂ is -NH₂;

(iii) NX₄X₅, where X₄ and X₅ are independently selected from the group consisting of hydrogen and saturated or unsaturated alkyl; and

(iv) halogen, wherein said R₅ is not chlorine or fluorine when R₂ is -NH₂;

(v) C(X₆)₃, where X₆ is selected from the group consisting of fluorine, chlorine, bromine, and iodine; and

(vi) OX₇, where X₇ is selected from the group consisting of hydrogen, saturated or unsaturated alkyl, and a five-membered or six-membered aryl or heteroaryl ring moiety; and

(b) collecting a precipitate comprising said compound.

37. The method of any one of claims 34, 35, or 36 wherein said first reactant and said second reactant are mixed in one or more solvents selected from the group consisting of dimethyl sulfoxide, potassium tert-butoxide, and sodium hydride.

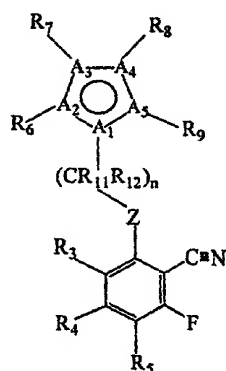
38. The method of claim 34, wherein said ZH moiety is isothiocyanate.

39. The method of claim 38, wherein said first reactant and said second reactant are mixed in dichloromethane.

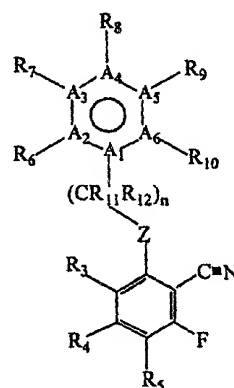
40. A method for synthesizing a compound of claim 25, comprising the steps of

(a) reacting a first reactant with a second reactant yielding said compound, wherein said first reactant is guanidinium carbonate, and wherein said second reactant has the structure set forth in formula XIX or XX:

(XIX)



(XX)



wherein,

(a) A_1 , A_2 , A_3 , A_4 , A_5 , and A_6 are independently selected from the group consisting of carbon, nitrogen, oxygen, and sulfur;

(b) R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , and R_{10} are

independently selected from the group consisting of:

(i) hydrogen, provided that at least one of R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , and R_{10} is a non-hydrogen moiety if R_2 is $-NH_2$;

(ii) saturated or unsaturated alkyl, wherein said R_8 is not methyl when R_2 is $-NH_2$ and when $n = 1$;

(iii) NX_2X_3 , where X_2 and X_3 are independently selected from the group consisting of hydrogen, saturated or unsaturated alkyl, and five-membered or six-membered aryl or heteroaryl ring moieties;

(iv) halogen or trihalomethyl, wherein said R_8 is not chlorine or fluorine when R_2 is $-NH_2$ and when $n = 1$;

(v) a ketone of formula $-CO-X_4$, where X_4 is selected from the group consisting of hydrogen, alkyl, and five-membered or six-membered aryl or heteroaryl moieties;

(vi) a carboxylic acid of formula $-(X_5)_n-COOH$ or ester of formula $-(X_6)_n-COO-X_7$, where X_5 , X_6 , and X_7 are independently selected from the group consisting of alkyl and five-membered or six-membered aryl or heteroaryl moieties and where n is 0 or 1;

(vii) an alcohol of formula $(X_8)_n-OH$ or an alkoxy moiety of formula $-(X_8)_n-O-X_9$, where X_8 and X_9 are independently selected from the group consisting of alkyl and five-membered or six-membered aryl or heteroaryl ring moieties and where n is 0 or 1, and wherein said ring moieties are optionally substituted with one or more

substituents selected from the group consisting of alkyl, halogen, trihalomethyl, carboxylate, and ester;

(viii) -NHCox_{10} , where X_{10} is selected from the group consisting of alkyl, hydroxyl, and five-membered or six-membered aryl or heteroaryl ring moieties, wherein said ring moieties are optionally substituted with one or more substituents selected from the group consisting of alkyl, halogen, trihalomethyl, carboxylate, and ester;

(ix) $\text{-SO}_2\text{NX}_{11}\text{X}_{12}$, where X_{11} and X_{12} are selected from the group consisting of hydrogen, alkyl, and five-membered or six-membered aryl or heteroaryl ring moieties;

(x) a five-membered or six-membered aryl or heteroaryl ring moiety optionally substituted with one or more substituents selected from the group consisting of alkyl, halogen, trihalomethyl, carboxylate, and ester moieties;

(f) any adjacent R_3 , R_4 , and R_5 or any adjacent R_6 , R_7 , R_8 , R_9 , and R_{10} are fused together to form a five-membered or six-membered aryl or heteroaryl ring moiety, wherein said five-membered or six-membered aryl or heteroaryl ring comprises two carbon atoms of the quinazoline ring;

(c) R_{11} and R_{12} are independently selected from the group consisting of

(i) hydrogen;

(ii) saturated or unsaturated alkyl; and

(b) collecting a precipitate comprising said compound.

41. The method of claim 40, wherein said first reactant and said second reactant are mixed in N,N-dimethylacetamide.

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